



COVID-19 vaccines: challenges and promises of trials, manufacturing and allocation of doses

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“Vaccine manufacturing challenges encourage a new form of knowledge-sharing that could boost progress and technological advances in the vaccine industry. Allocation of vaccine doses represents a real test bench for policy makers and industry leaders who pledged to equitable access.”

Tweetable abstract: Reflections on challenges and promises of COVID-19 vaccine development show opportunities for innovation and collaboration between stakeholders.

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Developing a vaccine against SARS-CoV-2 is one of the most time-pressured scientific challenges of our time. Working at unprecedented speed, more than 160 vaccine projects are in development, with 48 in clinical phases. The average vaccine takes 10.71 years to get from preclinical phases to market [1], for SARS-CoV-2, the timeline has been set to 12–18 months. Several candidates have managed to progress through preclinical and early clinical stages at this record speed. Three main challenges pave the way to successful vaccine deployment: proving efficacy in clinical trials; scaling-up manufacturing capabilities; and allocating vaccine resources globally.

These challenges require an ever-increasing collaboration between all stakeholders involved, from members of the scientific community and vaccine developers to policy makers and international organisations.

Clinical trials: rigor & transparency

Proving efficacy and safety through clinical trials is a crucial step in deploying safe and efficacious vaccines. Clinical trials for COVID-19 vaccines are faced with multiple challenges. First, the capacity to measure efficacy and safety is heavily dependent on ongoing SARS-CoV-2 transmission. As a consequence, successful efforts to suppress transmission with lockdowns and social distancing are at odds with a fast collection of efficacy and safety data. Therefore, large trials are required, and studies should be adequately powered. Multiple variables, including local transmission rates and participant profiles, should be deployed to inform power calculations [2]. Another hurdle is posed by the absence of validated surrogate end points. For instance, presence of antibodies has not been proven to be sufficient to prevent infection or disease symptoms. Moreover, there is a lack of standardization and harmonization of assays deployed in trials [3,4]. This can decrease the degree of reproducibility of efficacy data and may influence future comparisons of candidates.

The exceptional circumstances of the global COVID-19 pandemic are putting clinical trials under constant time pressure. Restricted timelines increase the risk of limited knowledge on the efficacy and safety of vaccines. This is not to be ascribed to trial misconduct or lack of scientific rigor, but to the uncontrollable variables of SARS-CoV-2 transmission and an incomplete understanding of its immunological features. Therefore, it is imperative that vaccine developers and scientists communicate the significance of clinical trial data with rigor and transparency. This is especially important considering that misleading and obsessive media coverage could set

unrealistic expectations. The management of scientific communication has never been more crucial and should aim to preserve the respectability and trust in vaccinations as a strategy for disease control.

Scaling-up manufacturing capabilities

As promising data on vaccine efficacy is released, vaccine developers are rushing to build manufacturing capacity. Based on the vaccination guidelines suggested by the WHO (Geneva, Switzerland), the initial vaccination strategy requires 4265 Mn doses of vaccine to protect at-risk populations [5]. It took 9 years to take the global production capacity of pandemic influenza vaccines from 1500 Mn doses in 2006 to 6400 Mn doses in 2015 [6]. Reaching similar results with SARS-CoV-2 candidates in a much shorter timeframe requires a considerable manufacturing effort, regardless of the vaccine type.

Synthetic manufacturing methods used for mRNA and DNA vaccines offer a streamlined manufacturing line and favourable characteristics, such as low batch-to-batch variability and more agile equipment; however, these methods have never been used to produce vaccines at large scale. On the other hand, cell-culture-based approaches used for live-attenuated virus vaccines, inactivated and subunit vaccines can rely on a much longer history of good manufacturing practices. However, cell-culture-based approaches entail several cell culture expansion and purification steps which are time consuming and require large-scale equipment. No single vaccine approach is currently emerging as a winner and it is likely that multiple safe vaccines will be approved. In fact, the diversity in vaccine technologies may provide the potential for scalable production required for widespread vaccine deployment [7].

The large demand for doses will likely require vaccine manufacturers to engage in collaborations and partnerships. In an initial call for collaboration, the WHO encouraged key stakeholders to voluntarily pool knowledge, data and intellectual property in the COVID-19 Technology Access Pool [8]. The initiative was received with resistance by the pharmaceutical industry, especially in the field of biologics and vaccine manufacturing where traditionally much of the knowhow is never publicly shared nor contained in patents [9], as it represents competitive advantage and is the result of considerable R&D investment. However, with increasing pressure on development pipelines, secrecy may hinder progress and some companies have started to seek knowledge transfer and sharing. Six biopharmaceutical companies working on monoclonal antibody candidates were recently granted permission by the US Department of Justice to exchange 'technical information' on each other's manufacturing processes and platforms under antitrust law [10]. Such knowledge transfer agreements may also occur among vaccine firms. It is likely that several manufacturers and developers will engage in various forms of licensing deals to produce enough doses of the candidates that prove efficacious. Moreover, several, if not all, of the funding provisions and advanced purchase commitments undersigned by various countries and organisations may already contain conditions that encourage knowledge sharing [11]. Overall, policy makers should facilitate and encourage knowledge sharing to produce vaccines as broadly and efficiently as possible.

Global strategies for allocation of vaccine resources

With the aim of mapping and planning vaccine production efforts, the Coalition for Epidemic Preparedness Innovations (Oslo, Norway) surveyed vaccine manufacturers and found production capacity to lie between 2 and 4 billion doses by the end of 2021, presuming clinical trials are successful. Airfinity (London, UK), a market analytics firm, projected that only 1 billion doses could become available by the end of 2021 after adjusting for vaccine developers' characteristics and chances of success [12]. Despite the efforts aimed at scaling up manufacturing capacity, vaccines will be scarce, especially in the first phases of deployment. Wealthy countries have already signed purchase commitments for more than 2 billion doses [12], limiting equitable access and international efforts for global allocation appear unsuccessful so far. Three main international allocation models have been proposed.

In the first model, the WHO suggested a population-proportional distribution model, starting with 3% of the population receiving vaccines and continuing with allocation until all countries have vaccinated 20% of their population [5]. In the second model, the WHO suggested allocation to be based on the number of frontline workers, incidence of comorbidities and proportion of the population over 65 years of age [5]. These two models present limitations. A population-proportional allocation system fails to consider differences in mortality and economic effects of COVID-19 in different countries. The second proposal may penalise low and middle-income countries which often have a younger population and fewer healthcare workers per capita [13]. The third model, the Fair Priority Model, strives to address some of the aforementioned limitations by using health and socioeconomic metrics to gauge and allocate vaccine doses based on quantified effects on health and economies [13]. Transmission

rates, standard expected years of life lost averted per dose of vaccine, absolute improvement in gross national income and reduction in the absolute size of the poverty gap per vaccine dose are used as allocation criteria. The WHO and World Bank (DC, USA) could play a crucial role in defining a framework to calculate these variables. Nevertheless, the Fair Priority Model is heavily dependent on the integrity and transparency in data reporting and analysis.

A possible solution to ensure further cooperation and transparency could be to create an international multi-tasking platform coordinating contracts between pharmaceutical companies, contractors, distributors, governments and donors. The platform could be supervised by an international entity, such as the WHO, and it would work at its full potential if funding provisions from governments and other donors could be allocated exclusively to the companies that partake in the platform. For the pharmaceutical companies involved, partaking into the platform ensures that their capabilities are saturated and that they have a clear timeline of commitments. If their candidate fails, then they would be automatically enrolled as a vaccine manufacturer that can license-in a successful vaccine compatible with their production capabilities. For governments, allocating funds to a platform with a wide vaccine portfolio decreases the risks of failure connected to engaging only with few vaccine producers whose candidates may fail.

Conclusion

In the quest for a vaccine, all stakeholders have a fundamental role to play. Defining harmonized efficacy end points and communicating significance of trial findings requires an unprecedented collaboration between the scientific community, vaccine developers and regulators. Vaccine manufacturing challenges encourage a new form of knowledge-sharing that could boost progress and technological advances in the vaccine industry. Allocation of vaccine doses represents a real test bench for policy makers and industry leaders who pledged to equitable access. Several health economics metrics can inform strategies and aid decision-making. Ultimately, in a global pandemic, losses and gains will be indiscriminately distributed over all countries and individuals involved.

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